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Ciproxifan improves working memory through increased prefrontal cortex neural activity in sleep-restricted mice

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ABSTRACT

Histamine receptor type 3 (H3) antagonists are promising awakening drugs for treatment of sleep disorders. However, few works have tried to identify their cognitive effects after sleep restriction and their impact on associated neural networks. To that aim, Bl/6J male mice were submitted to acute sleep restriction in a shaker apparatus that prevents sleep by transient (20–40 ms) up and down movements. Number of stimulations (2–4), and delay between 2 stimulations (100–200 ms) were randomized. Each sequence of stimulation was also randomly administered (10–30 s interval) for 20 consecutive hours during light (8 h) and dark (12 h) phases. Immediately after 20 h-sleep restriction, mice were injected with H3 antagonist (ciproxifan 3 mg/kg ip) and submitted 30-min later to a working memory (WM) task using spatial spontaneous alternation behaviour. After behavioural testing, brains were perfused for Fos immunohistochemistry to assess neuronal brain activation in the dorsal dentate gyrus (dDG) and the prefrontal cortex. Results showed that sleep restriction decreased slow wave sleep (from 35.8 ± 1.4% to 9.2 ± 2.7%, $p < 0.001$) and was followed by sleep rebound (58.2 ± 5.9%, $p < 0.05$). Sleep restriction did not modify anxiety-like reactivity and significantly decreased WM at long (30 s) but not short (5 s) inter-trial intervals. Whereas sleep restriction failed to significantly modify immunopositive cells in vehicles, ciproxifan administration prevented WM deficits in sleep restricted mice through significant increases of Fos labelling in prelimbic, infralimbic and cingulate 2 cortex.

In conclusion, ciproxifan at 3 mg/kg enhanced WM in sleep restricted mice through specific modulation of prefrontal cortex areas.

1. Introduction

Ciproxifan (cyclopropyl 4-(3-(1H-imidazol-4-yl)propyloxy) phenyl ketone) is an extremely potent histamine H_3 receptor inverse agonist/antagonist. The histamine H_3 receptor is an inhibitory autoreceptor located on histaminergic nerve terminals, and is involved in modulating the release of histamine in the brain. Histamine has an excitatory effect in the brain via H_1 receptors in the cerebral cortex, and so drugs such as ciproxifan which block the H_3 receptor and consequently allow more histamine to be released have an alertness-promoting effect (Le et al., 2008; Ligneau et al., 1998; Parmentier et al., 2002; Vanni-Mercier et al., 2003). Interestingly, H3 receptors are also found on cholinergic and dopaminergic neurons, and therefore modulate the release of several neurotransmitters. Therefore, histaminergic neurons are involved in cognitive processes such as memory mainly via the interaction with the cholinergic system and/or the activation of H1 and H2 receptors of the cerebral cortex or the hippocampus. Antagonists of H3 receptors such as ciproxifan or thioperamide produces wakefulness in animal studies and also produces cognitive and memory enhancing effects mainly the consolidation phase of memory processes (Alvarez and Banzan, 2008; Benetti and Izquierdo, 2013; Bonini et al., 2013; Da Silveira et al., 2013; Köhler et al., 2011). It has been also found that thioperamide could enhance spontaneous alternation involving spatial working memory (Vohora et al., 2005) and counteract the memory impairments induced by anticholinergic compounds such as scopolamine (Bernaerts et al., 2004; Komater et al., 2005; Miyazaki et al., 1995; Orsetti et al., 2001; Xu et al., 2009).

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From a functional viewpoint, specific neurocognitive domains including executive attention, working memory and higher cognitive functions are particularly vulnerable to sleep loss (Durmer and Dinges, 2005; Mu et al., 2005). More specifically, sleep loss, even moderate, compromises the function of neuronal circuits critical to sub second attention processes during working memory tasks (Smith et al., 2002). The associated decrease in brain activity during working memory tasks appears to be a function of the individual sleep restriction vulnerability. Moreover, executive functioning is largely dependent on activity in the prefrontal cortex and affected negatively by one night sleep restriction (Chee et al., 2006; Chuah et al., 2006; Killgore et al., 2006; Leenaars et al., 2012; Libedinsky et al., 2011; Nilsson et al., 2005). Hippocampus-dependent memory and plasticity are also impaired after sleep restriction (Guan et al., 2004; Hagewoud et al., 2010; Hairston et al., 2005; McDermott et al., 2003; Romcy-Pereira and Pavlides, 2004; Tung et al., 2005; Vecsey et al., 2009).

Survey of the studies has thus clearly established a wakening impact of H3 antagonist in sleep-restricted subjects (Iannone et al., 2010; James et al., 2011; Wallace et al., 2011) or a cognitive enhancing effects in non sleep-restricted subjects. However, to the best of our knowledge, there is no study having as yet investigated the effect of H3 receptor antagonist on working memory after sleep restriction and related brain neural activity. Hence, the original aims of our study have been to investigate in sleep-restricted mice, the effects of ciproxifan on spatial working memory with subsequent evaluation of the neural activity level in various cerebral areas known to be involved in working memory such as the prefrontal cortex and hippocampus (Beracochea and Jaffard, 1985; Pierard et al., 2007; Vandesquille et al., 2013).

2. Materials and methods

2.1. Animals

Subjects were male mice of the C57Bl/6J inbred strain obtained from Charles Rivers (France). They were either 3 months at the time of experiments, and housed individually with continuous access to food and water, on a 12 h light–dark cycle (light onset: 8 am; offset: 8 pm) in a temperature-controlled room. All test procedures were conducted during the light phase of the cycle. Experiments were performed respecting the new European Communities Council Guidelines (Directive 2010/63/EU). Protocols were approved by an independent ethical board (authorization number: IMASSA_Chauveau1101).

2.2. Apparatus for alternation task

Behavioural tests were conducted in a grey Plexiglas T-maze. Stem and arms were 35 cm long, 15 cm wide and 10 cm high. The starting box (10 cm × 12 cm) and each goal-arm were separated from the central alley by a vertical sliding door, with opening and closing monitored by a computer (Imetronic, France). Photoelectric cells allow recording of both the choice of the goal-arm (left or right) and the latency (in sec) that elapsed between the opening of the start-box and the closing of the goal-box. The T-maze was located at the centre of a room with various allocentric cues (white or black or striped card boards) located on the wall 1 m above the apparatus. A white noise (30 dB) and controlled lighting (30 lux) were also provided in the behavioural testing room.

2.3. Behavioural procedure

The behavioural task used to test working memory (WM) is based on spontaneous alternation behaviour (SA), which does not require the use of food reinforcement to emerge. SA is the innate tendency of rodents whereby over a series of trials run in a T-maze, they alternate at each successive trial the choice of the goal arm (except for the first trial). From trial to trial, accurate performance at a given trial (N) requires for subjects to be able to discriminate the specific target trial N-1 from the interfering trial N-2. Thus, the target information required for successful performance varies from trial to trial, so that the subject is not only required to keep temporarily in short-term memory specific information, but also to reset it over successive runs. The resetting mechanisms and cognitive flexibility required to alternate over successive runs are major components of working memory processes. Working memory is a component of the sequential alternation task, since SA rates are dependent on the length of the inter trial delay interval, and/or the place of the trial in the series. Indeed, repetitive testing constitutes a potent source of proactive interference. Thus, the sequential alternation procedure is relevant to assess delay-dependent working memory in mice (Beracochea and Jaffard, 1985; Chauveau et al., 2005; Vandesquille et al., 2013). Animals were not food restricted and no food reinforcement was used. Animals were first submitted to a habituation phase consisting in 2 free exploration sessions 10 min each, over 2 consecutive days (one session per day, Day 1 and Day 2) in the apparatus with all doors opened. At the end of the habituation phase, all subjects were submitted to a training phase, involving a series of 6 successive trials separated by a 30 s inter-trial interval (ITI). The training phase was aimed at familiarizing the subjects with the opening and closing of the doors.

The behavioural schedule was identical for the training phase and test session. Thus, in both cases, the subject was placed in the start box at the beginning of a trial, and after a confinement period (predefined ITI) the door to the stem was opened. When the mouse entered one of the arms, the door was closed, and the chosen arm was recorded. After a 30 s confinement period in the chosen arm, the mouse was gently returned to the start-box for a second trial, identical to the first one. In the test session however, animals of independent groups were submitted to the same general procedure as in the training phase, except that the ITI was either 5 s or 30 s. The parameters recorded for the analysis of each trial were the chosen arm and the running latency (time between the start arm and the chosen arm). Alternation rates and running latency were averaged for 6 consecutive trials.

To avoid olfactory cues in the apparatus, visible traces of urine and faeces were removed from the apparatus between trials and the maze was cleaned with 5% ethanol solution.

The sleep restriction procedure was interpolated between the training phase (Day 3) and the test phase (Day 4).

2.4. Elevated plus maze

The plus-maze, which was constructed of grey Plexiglas, consisted of four arms arranged in the shape of a plus sign. Each arm was 30 cm long, 7 cm wide and elevated 38 cm above the ground. The four arms were joined at the centre by a 7-cm square platform. Two opposite arms of the plus maze were “closed” by side walls 24 cm high, but open on the top, while the remaining arms did not have side walls. Light intensity was controlled before experiment (100 lux in open arms; <10 lux in closed arms). These walls did not extend from the centre of the maze. At the beginning of each test, mice were placed on the centre of the maze and were allowed to freely explore all arms of the maze for 5 min. Behaviour was recorded by video tracking system (Viewpoint, France) allowing to measure the travelled distance (in cm) and running time (s) into both the open and closed arms. Entry and latency were recorded only when a mouse entered an arm with all four paws. Two measures of “anxiety” were taken. The first was the ratio of the time spent in the open arms divided by the total time spent in all arms of the maze (time ratio). The second was the ratio of distance into the open arms divided by the total distance in all arms (distance ratio). Thus, the smaller are these ratios, the more “anxious” is the mouse. This experiment was performed in animals being either non sleep deprived, or having been submitted to a 20 h-sleep restriction procedure, as described below. Behavioural testing occurred immediately after the end of the sleep restriction phase as for working memory experiment.

2.5. Sleep deprivation procedure

2.5.1. Apparatus and general schedule

Mice were submitted to acute sleep deprivation in a shaker apparatus (PVC cylinder, diameter 30 cm, 45 cm height) that prevent sleep by transient up and down movement (20–40 ms, 1 cm height). Number of stimulations (2–4) and delay between 2 stimulations (100–200 ms) were randomized and controlled by software (Viewpoint, France). Each sequence of stimulation were also randomly administered (10–30 s interval) for 10 (zeitgeber time: ZT15-ZT24) or 20 consecutive hours (ZT5-ZT24).

2.5.2. Validation of sleep deprivation model by polysomnographic recordings

EEG and EMG electrodes were implanted under deep anaesthesia with a mixture of ketamine and xylazine (100 mg/kg and 10 mg/kg *ip* respectively). Three stainless steel miniature screws (diameter: 520 μm) were implanted in contact with dura matter and served as frontal electrode (stereotaxic coordinate bregma as a reference: AP = +2 mm, LAT = +1 mm), parietal electrode (AP = −2 mm, LAT = −1.5 mm) and reference electrode (AP = −6 mm, LAT = +2 mm). Screws were soldered to Teflon® coated semi-rigid silver wires (330 μm in diameter) connected to a female contact (MS363, PlasticOne) that was inserted to a pedestal (E363, PlasticOne). For EMG recordings, two semi-rigid silver wires (330 μm in diameter) served as EMG electrodes and were connected to a female contact and inserted into the pedestal. Screws and pedestal were fixed to the skull with glass ionomer cement (GC FujiPlus, USA). Animals were allowed to recover during 10 days. EEG and EMG recordings were performed using Epas40 hardware (Deltamed, France) at a 256 Hz sampling rate. Mice were habituated to the shaker environnement during 24 h (day 1), day after, recordings were performed to get 24 h baseline polysomnographic recordings (day 2). On day 3, animals were sleep-deprived during 20 h consecutively (from ZT5 to ZT24). On day 4, the shaker was switched off (ZT0), animals were free to sleep *ad libitum* and sleep rebound was quantified (ZT0-ZT4).

Sleep-wake states were scored by off-line semi-automated analysis, as described in detail elsewhere (Gervasoni et al., 2004). Three main stages were scored each 5 s epochs: WAKE (high and variable amplitude EMG, and a low voltage, fast activity EEG, with theta rhythm during exploratory behaviour), SWS (slow wave sleep; low amplitude EMG with no phasic events, and a high voltage EEG with slow waves (1–4 Hz) and spindles (10–14 Hz) and PS (paradoxal sleep; very low voltage EMG, and a low voltage EEG with a marked periodicity in the theta band (5–9 Hz)).

2.6. Immunohistochemical procedure

90 min after the beginning of alternation test, mice were anaesthetized (ketamine 100 mg/kg + xylazine 10 mg/kg; injected volume: 0.1 ml/10 g mouse). They were then perfused into aorta with 25 ml NaCl 0.9% followed by 25 ml paraformaldehyde 4% to fix tissue before the brain was removed. Fixed brains were cut in frontal sections of 50 μm each using a vibratome (Leica 1600S, Germany). Sections were incubated with a primary antibody specific of Fos protein (PC38, Calbiochem), then with a biotinyled secondary antibody (Interchim), and finally with the avidine-biotine-peroxydase complex Vectastain® (Abcys). C-Fos immunoreactivity was revealed using NovaRed® peroxydase substrate kit (Vector Laboratories). Different brain areas were manually quantified using with the image analysis system Histolab® (Microvision Instruments, France) coupled with a microscope. The analysis concerned the main brain areas involved in spatial working memory including prefrontal cortex (PrL for prelimbic area, Il for infralimbic area, Cg 1–2 for cingular cortex 1 and 2) and hippocampus (dDG/vDG for dorsal/ventral part of dentate gyrus, CA1/CA3 for Cornu Ammonis 1/3).

The quantification of Fos-positive nuclei in the studied brain regions following the alternation task was expressed in mean counts/mm^2 (5/6 animals/group, 3 slices/animal) in relative variations as compared to naïve controls (no treatment, no behaviour). ANOVA was used to evaluate significant effect of ciproxifan and/or sleep deprivation on Fos expression followed by Dunnet post hoc test. Significance was accepted at p values below 0.05.

2.7. Drug administration

Mice were daily handled for restraint habituation during 5 consecutive day. On day 3 (alternation test before sleep deprivation), all animals were intraperitoneally vehicle-injected 30 min before the first alternation trial (0.9% saline solution; 0.1 ml/10 g body weight). On day 4, after 20-h sleep deprivation and 30 min before the first alternation trial, mice were injected either by vehicle (0.9% saline solution), either ciproxifan solution (3 mg/kg body weight diluted in a 0.9% saline solution).

2.8. Statistics

Results are calculated as mean ± s.e.m. and expressed as percentages. The number of animals for each group is mentioned in the figure legends. Sleep stage scoring was compared using Student paired t-test (comparison between baseline *versus* sleep restriction; baseline *versus* sleep rebound; each animal is its own control). For behavioural and immunohistochemistry data, between-group effect were analysed one or two-way factorial ANOVA followed when required by post hoc comparisons (Dunnett's multiple comparison test). The significance level was set at $p < 0.05$, non-significant analyses are mentioned as "NS". Statistical analysis was performed using Statistica® 8.0. software.

3. Results

3.1. Polysomnographic validation of the sleep restriction model

Sleep restriction efficiency was evaluated by comparing spent time in slow wave sleep (SWS) and paradoxal sleep (PS) during baseline recordings, sleep restriction and sleep rebound (4 h after the end of sleep restriction; Fig. 1). Sleep restriction significantly decreased spent time in SWS (from 35.8 ± 1.4% to 9.2 ± 2.7%, $p < 0.001$) and PS (from 9.5 ± 2.4% to 0.03 ± 0.01%, $p < 0.05$). Moreover, increases of spent time in SWS (from 33.5 ± 2.6% to 58.2 ± 5.9%, $p < 0.05$) and PS (from 4.6 ± 1.3% to 16.1 ± 2.1%, $p < 0.05$) were observed after the end of sleep restriction protocol when animals were allowed to sleep (sleep rebound).

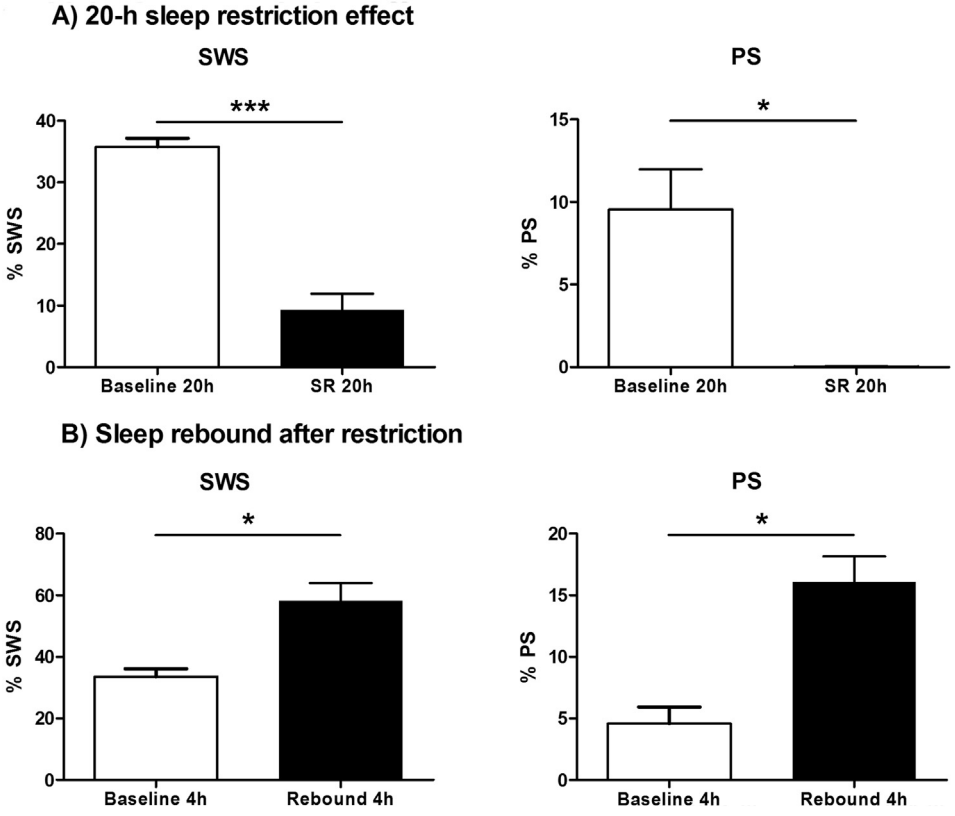

Fig. 1. Sleep restriction efficiency on sleep stages and sleep rebound A) 20-h sleep restriction effect. % of spent time in slow wave sleep (SWS; left histograms) and paradoxal sleep (PS; right) during baseline and sleep restriction (histograms represent 20 h-mean ± s.e.m. during ZT4-ZT24, $n = 5$ animals) : sleep restriction effect (paired t-test) : *** : $p < 0.001$; * : $p < 0.05$; B) Sleep rebound. % of spent time in SWS (left histograms) and PS (right) during baseline and sleep rebound (histograms represent 4 h-mean ± s.e.m. during ZT1-ZT4): sleep rebound effect (paired t-test): * : $p < 0.05$. Histograms represent mean ± s.e.m. of 5 animals.

3.2. Sleep restriction and spontaneous alternation

Spontaneous alternation rates were first evaluated after 10 or 20 h-sleep restriction by 6 consecutive alternation trials separated with an inter trial interval (ITIE) of 30 s (Fig. 2A). Between-group comparison using one way ANOVA showed that sleep restriction induced a decrease of alternation rate which was dependant of on the duration of the sleep restriction length ($F_{2,\ 43} = 14.18$, $p < 0.001$). More specifically, 20 h-restricted animals exhibited spontaneous alternation (SA) rates below those displayed by non-sleep restricted (NR) control mice (post hoc Dunnet's comparison: $p < 0.001$) and also by 10 h-restricted mice ($p < 0.01$). Group performance were analysed using 1-sample t test and were compared to the chance level (alternation rate = 50%). We observed that alternation percentages were above chance levels only for non-restricted (NR) control animals (77.14 ± 4.62%; $t = 5.874$, df = 13, $p < 0.0001$) and 10 h-SR mice (68.33 ± 2.93%; $t = 6.167$, df = 11, $p < 0.0001$). In contrast, after 20 h sleep restriction, behavioural performance were near chance level (46.67 ± 4.57%; $t = 0.7289$, df = 17, ns). The present data showed that long (20 consecutive hours) but not short (10 h) total sleep restriction efficiently impaired spatial working memory in a spontaneous alternation task. 20-h sleep restriction protocol was then used for further experiments.

Spontaneous alternation is a spatial working memory test that is dependent on delay (temporal gap) between trials or retention time (Beracochea and Jaffard, 1985; Chauveau et al., 2005; Vandesquille et al., 2013). Then, to test the temporal dependency of sleep restriction, we performed alternation task with ITI = 5 s and ITI 30 s on independent groups of mice (Fig. 2B). A two way ANOVA showed a significant interaction between sleep restriction and ITI (sleep restriction and ITI as factors: $F_{1,\ 44} = 9.0$, $p < 0.01$). More precisely, alternation performances were not altered by 20 h-SR with 5 s-ITI (Dunnett's comparison between NSR and SR group in 5 s-ITI experiment; NS) but significantly lowered for 30 s-ITI ($p < 0.001$). Interestingly, alternation performances in sleep-restricted animals were significantly above chance level for 5 s-ITI (76.00 ± 6.53%, $p < 0.01$) but not for 30 s-ITI (43.75 ± 4.55, NS).

3.3. Sleep restriction and elevated plus maze

SR mice showed no between groups difference on distance travelled in open-arms (NSR: 380.0 ± 71.9 cm *versus* SR : 434.4 ± 66.0; $t = 0.5578$, NS) nor in closed arms (NSR : 843.7 ± 83.2 cm *versus* SR : 1083.0 ± 77.9 cm; $t = 2.099$, NS). Similarly, no significant difference was observed in percentage of time spent in open arms (SR: 29.63 ± 3.58%; NSR : 28.22 ± 4.54%; $t = 0.2435$, NS).

3.4. Ciproxifan and spontaneous alternation after sleep restriction

Ciproxifan was administered immediately after sleep restriction 30 min before alternation test (Fig. 3). Running latencies did not differ between groups (2-way ANOVA with sleep restriction and injection as variance factor: $F_{1,\ 57} = 2.85$, NS; NSR vehicle: 16.85 ± 5.04 s; SR-20 h: 11.65 ± 3.45 s; NSR ciproxifan : 16.09 ± 5.22 s; SR-20 h ciproxifan: 16.31 ± 6.76 s; data not shown).

A global ANOVA on alternation rates showed a significant interaction between injection and sleep restriction as variance factors (two way ANOVA: $F_{1,\ 57} = 8.85$, $p < 0.01$). More precisely, in vehicle-treated animals, sleep-restricted animals exhibited performances below those displayed by control (non-sleep restricted) animals ($F_{1,\ 30} = 21.3$, $p < 0.001$). In contrast, no sleep restriction effect was found in ciproxifan-injected mice ($F_{1,\ 27} < 1.0$). Ciproxifan administration significantly increased alternation rates in sleep-restricted animals ($F_{1,\ 30} = 10.2$, $p < 0.01$). Vehicle non-restricted mice and both groups of ciproxifan-injected animals (non-restricted and 20 h-restricted animals) performed above chance level (77.14 ± 4.62%, $t = 5.874$; $p < 0.001$; 69.33 ± 5.81%, $t = 3.327$; $p < 0.01$ and 70.0 ± 5.84%, $t = 3.427$; $p < 0.001$ respectively) whereas vehicle sleep-restricted group did not (46.67 ± 4.57%, $t = 0.729$; NS).

Proactive interference is a cognitive process known to impair working memory in the last trials of a behavioural session. Interestingly, sleep-induced behavioural impairments were observed only in the last trial in vehicle-injected group (Fig. 3C: $F_{1,\ 30} = 5.77$; $p < 0.05$) but not in the first trial ($F_{1,\ 30} = 1.08$, NS, Fig. 3B).

3.5. Ciproxifan and neural activity involved in spontaneous alternation

Main areas of prefrontal cortex (PrL for prelimbic area, Il for infralimbic area, Cg 1–2 for cingular cortex 1 and 2) and hippocampus (dDG/vDG for dorsal/ventral part of dentate gyrus, CA1/CA3 for Cornu Ammonis 1/3) were analysed after behaviour using *ex vivo* Fos immunohistochemistry. Among these brains areas, only PrL, Il and Cg2 analysis showed significant modifications induced by ciproxifan injection or sleep restriction (Fig. 4).

Ciproxifan injection significantly increased Fos expression in PrL and Cg2 (injection effect of the two-way ANOVA: $F_{1,\ 15} = 17.10$, $p < 0.001$ and $F_{1,\ 15} = 11.96$, $p < 0.01$ for PrL and Cg2 respectively). Inter-group analysis revealed a significant ciproxifan-induced increase of Fos immunopositive cells in PrL in sleep-restricted animals (20.48 ± 2.06 *versus* 10.48 ± 1.82, Dunnet's post hoc test: $p < 0.01$; 20.48 ± 2.06 *versus* 10.18 ± 1.42, $p < 0.01$ for vehicle NSR and vehicle SR-20 h group respectively). Similarly, ciproxifan increased the number of immuno-positive cells in Cg2 in NSR

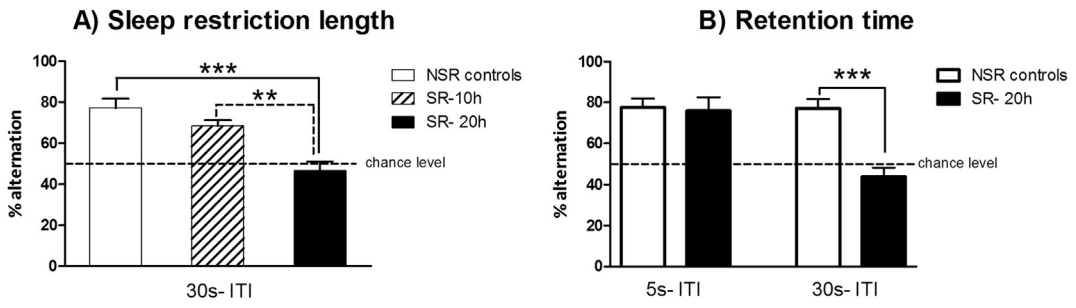

Fig. 2. Sleep restriction induces delay-dependent working memory deficits A) Effect of sleep restriction length % alternation represents means ± s.e.m. of 6 consecutive trials (inter-trial interval (ITI) = 30 s). NSR = non sleep restricted ($n = 14$); SR-10h = 10 h-sleep restricted ($n = 12$); SR-20 h = 20 h-sleep restricted ($n = 18$). B) Delay-dependent effect of sleep restriction % alternation represents means ± s.e.m. of 6 consecutive trials for inter trial interval (ITI) = 5 s (left histograms) and ITI = 30 s (right histograms). NSR = non sleep restricted ($n = 8$ and $n = 10$ for 5 s and 30 s-ITI respectively); SR-20 h = 20 h-sleep restricted ($n = 14$ and $n = 16$). Dotted lines represent random alternation (50% chance level). Between-group comparison (Dunnet's post hoc t test : ***: $p < 0.001$).

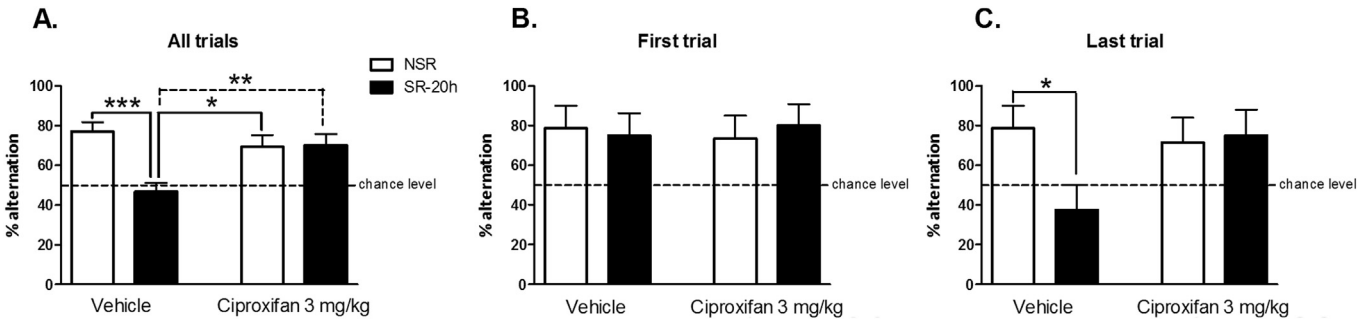

Fig. 3. Ciproxifan improves alternation rates in sleep-restricted animals % alternation (inter-trial interval (ITI) = 30 s) represents means ± s.e.m. of 6 consecutive trials (all trials, A; left histograms), the first (B) and the last trial (right histograms; C). NSR = non sleep restricted ($n = 14$ and $n = 15$ for vehicle and ciproxifan-injected animals respectively); SR-20 h = 20 h-sleep restricted mice ($n = 18$ and $n = 14$). Between-groups comparison Dunnet's post hoc t test: ***: $p < 0.001$, **: $p < 0.01$, *: $p < 0.05$).

(67.92 ± 15.20 *versus* 24.99 ± 8.36, $p < 0.05$) and SR-20 h group (62.23 ± 10.26 *versus* 24.99 ± 8.36, $p < 0.05$).

Sleep restriction modulated Fos expression for infralimbic cortex (sleep effect on the 2-way ANOVA: $F_{1, 17} = 7.83$, $p < 0.01$) and dDG (sleep restriction effect of the two-way ANOVA: $F_{1, 16} = 5.25$, $p < 0.05$). Dunnet's post hoc analyses revealed that sleep restriction induced a significant increase of Fos-positive cells in Il (infralimbic cortex) of ciproxifan-injected animals (13.17 ± 2.44 *versus* 29.39 ± 4.28; $p < 0.01$) but only a non-significant tendency in dDG in vehicle-injected animals (2.55 ± 0.28 *versus* 3.85 ± 0.68).

4. Discussion

The main results of the study are as follows: i) sleep restriction significantly decreased slow wave sleep (from 35.8 ± 1.4% to 9.2 ± 2.7%, $p < 0.001$) and was followed by significant sleep rebound (58.2 ± 5.9%, $p < 0.05$). Sleep restriction did not modify anxiety-like reactivity in the elevated plus-maze nor running latencies in the T-maze but significantly impaired working memory (WM) at long (30 s) but not short (5 s) inter-trial intervals. WM impairments were mainly observed at the end of the test session, i.e. when proactive interference effect is high. Whereas sleep restriction failed to significantly modify immunopositive cells in both the hippocampus and the prefrontal cortex, ciproxifan administration prevented WM deficits induced by sleep restriction through a significant increase of Fos labelling notably in the prelimbic, the infralimbic and cingular corteces.

The WM impairments observed in our study after a long-term (20 h) sleep restriction is in agreement with a previous study of our team, even though involving another sleep restriction procedure (Pierard et al., 2007) and with another study (Hagewoud et al., 2010). Interestingly, a shorter (10 h) sleep restriction did not impair WM as previously shown (6 h sleep restriction; see Hagewoud et al., 2010; Ramanathan et al., 2010). The increase of interference has been also reported in clinical studies showing that sleep restriction could impair memory functions by increasing false memories and intrusions (Diekelmann et al., 2008) and in subjects suffering from primary insomnia (Drummond et al., 2013).

Besides pharmacological means (for example monoamine oxidase inhibitors that completely suppresses paradoxical sleep; see Vogel et al., 1990; Watts et al., 2012; Wichniak et al., 2012) or gentle handling (Palchykova et al., 2006), several sleep restriction apparatuses (mainly for rats or bigger animals) are described in the literature (Caron and Stephenson, 2010; Christie et al., 2008; Everson et al., 1994; Kim et al., 2007; Leenaars et al., 2011; Rechtschaffen and Bergmann, 2002; Vogel, 1975). Furthermore, some of them allow selective REM (rapid eye movement sleep or paradoxical sleep (PS)) or non-REM (or slow waves (SWS) sleep restriction, with the help of polygraphic recordings. The sleep restriction procedure used in our study did not target a specific type of sleep (SWS *versus* PS). Indeed, the sleep restriction procedure used in our study induced a significant and substantial reduction of both SWS and PS, as compared to non sleep-restricted mice. The severity of the sleep restriction in our procedure is also confirmed by the observation of a rebound effect on both types of sleep, which is a well known compensatory phenomenon observed after sleep restriction in mammals (Cirelli and Tononi, 2008; Siegel, 2005).

In our study, we used Fos marker to target neural activity in sleep restricted mice. Fos is the protein product of the immediate early gene c-Fos. In response to a stimulus, one observes first an increase in c-Fos mRNA levels, which is soon followed by a maximal expression of Fos protein 90 min after cell stimulation (Bisler et al., 2002). Fos protein is a transcription factor that, by binding to DNA regulatory regions, can control the expression of many "target" genes. The expression of Fos protein is classically considered as a relevant indicator of neural activity (Herrera and Robertson, 1996; Sheng and Greenberg, 1990). In sleep-restricted rats, c-Fos expression in several brain areas is higher with respect to control animals (Cirelli et al., 1995). Indeed, after a few hours of spontaneous waking or sleep restriction, c-Fos and other IEGs is high in cerebral cortex, hypothalamus, septum, and several thalamic and brainstem nuclei (Cirelli and Tononi, 2000). In addition, a significant increase in c-Fos mRNA in mouse was found in cerebral cortex, basal forebrain, thalamus and cerebellum following a 6-h sleep restriction (Terao et al., 2003). Contrariwise the expression of c-Fos in mouse brain is very low after a few hours of sleep/inactivity (Basheer et al., 1997). Considered together, these results indicate that c-Fos expression is associated with waking, but is not proportional to the amount of previous waking (Cirelli and Tononi, 2000). Interestingly, in contrast to the present study, it is noteworthy that none of the above studies submitted animals to a behavioural task before Fos analysis and such a procedural difference could explain those discrepancies.

After a 20-h sleep restriction period followed by behavioural testing, we evidenced no significant increase in Fos staining in hippocampus regions (dDG, CA1 and CA3), nor in the mPFC (cingular, infralimbic and prelimbic cortices). Insofar as Fos is measured after the WM memory task, it is thus possible that the sensibility of the hippocampus and mPFC regions to sleep restriction could be modified by the neural activation induced by the WM task which follows the sleep restriction phase, rendering difficult to detect a significant deleterious impact of sleep restriction on neural activities in these brain areas, known to be particularly involved in the alternation task and impaired by sleep restriction. Indeed, we reported here that the 20-h sleep restriction period induced WM impairments which depended on both the length of the inter-trial intervals and the place of the trials in the series (see also Pierard et al., 2007). More specifically, whereas no WM deficit was

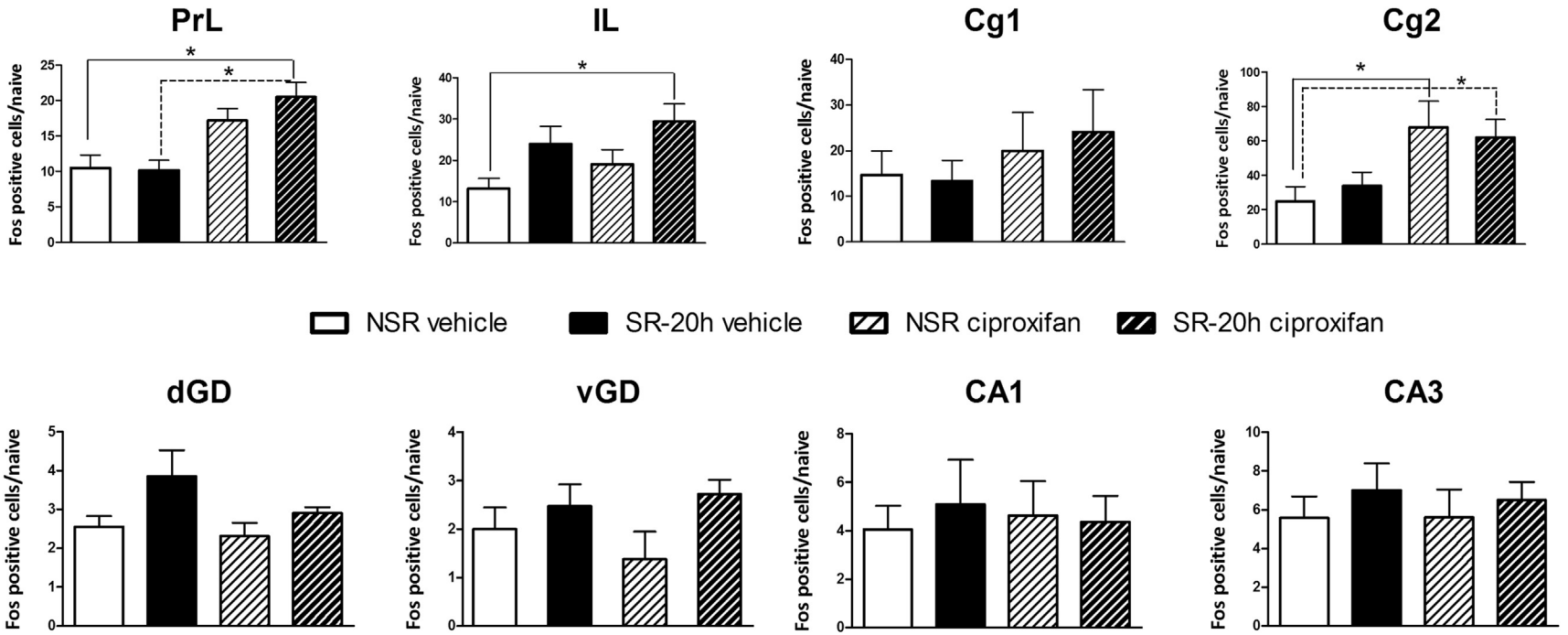

Fig. 4. Ciproxifan and neural activities in prefrontal cortex and hippocampus Numbers of Fos positive cells are expressed in relative value compared to naive (non-behaving animals). PrL: prelimbic cortex, Il: infralimbic cortex, Cg 1–2 : cingular cortex 1–2, and dDG/vDG: dorsal/ventral part of dentate gyrus, CA1/CA3 : Cornu Ammonis 1/3 of hippocampus. Values represent means ± s.e.m. of each group : NSR = non sleep restricted (vehicle: 18 brain slices/6 animals; ciproxifan : 15 brain slices/5 animals), SR-20 h = 20 h-sleep restricted (vehicle : 15 brain slices/5 animals; ciproxifan : 18 brain slices/6 animals). Dunnet's post hoc *t* test : **: $p < 0.01$, *: $p < 0.05$.

observed when the inter-trial interval was short (5 s), a severe WM deficit was observed when the inter-trial interval was increased to 30 s. Thus, the WM deficit is mainly observed for the last trials of the series, suggesting that sleep restriction increased the sensitivity to delay-dependent proactive interference. The fact that the impairment of alternation behaviour is not observed at a short inter-trial interval discards the hypothesis that the WM deficit of sleep restricted mice would be due to a progressive loss of motivation for alternation, or from sensory-motor impairments, as also indicated by similar running latencies in sleep and non-sleep restricted animals. Interestingly, it has been found that processes subserved by dDG include pattern separation of spatial information, involving the reduction of interference between similar spatial locations (Kesner, 2013; see also Newmark et al., 2013). Conversely, the improvement of WM in sleep restricted mice after ciproxifan administration is associated from a cognitive point of view to a reduction of interference among trials, and from a neurobiological point of view, to a tendency of reduction of Fos immunopositive cells in dDG, which may indicate that ciproxifan restores normal molecular cascades in this brain region. This hypothesis fits well with neuroanatomical and biochemical studies evidencing high levels of H3 receptors in the dentate gyrus in mice (Chazot and Hann, 2001) and rats (Pillot et al., 2002).

In contrast to the reduction of Fos labelling observed in dDG, ciproxifan significantly increased Fos expression in the mPFC. The mPFC has been also found to be implicated in WM, and more particularly in maintaining information in short-term memory and in managing interference on a short-term span (Dalley et al., 2004; Delatour and Gisquet-Verrier, 1999; Granon et al., 1994; Kesner and Churchwell, 2011; Kesner et al., 1996; Thuault et al., 2013). In agreement with these studies, we already reported that neuronal inhibition by lidocaine infusion into the mPFC of mice appeared deleterious on WM in the spatial alternation task (Vandesquille et al., 2013). Thus, the WM improvement in ciproxifan-treated mice is also due to an enhancement of mPFC functions, in parallel to its action on dDG. Indeed, ciproxifan has been reported to improve attentional processes (Ligneau et al., 1998) which are substantially subserved by the frontal cortex activity. In addition, the effect of ciproxifan on Fos expression in the mPFC is in agreement with studies also evidencing high densities of H3 receptors in the frontal cortex (Hamill et al., 2009). It has been reported that compounds acting on histamine receptors substantially improve memory processes. Thus, more specifically, thioperamide (a potent antagonist) or (R)alphamethylhistamine (a potent agonist), both being highly selective *versus* the H1 and H2 receptors (Köhler et al., 2011) or ciproxifan (H3R antagonist) and pitolisant (a H3R antagonist/inverse agonist) mediate their procognitive effects via their impact on the release of a large number of neurotransmitters in both the frontal cortex and the hippocampus, such as dopamine and acetylcholine (for review, see Schwartz, 2011). Nevertheless, a specific contribution of the present study is to evidence that the procognitive impact of ciproxifan result from bidirectional impact on Fos labelling in the mPFC (enhancement) and dDG (decrease). By and large, this study emphasized the usefulness of histaminergic compounds to enhance cognitive functions in tasks recruiting the prefrontal cortex.

5. Conclusion

Ciproxifan 3 mg/kg has an enhancing effect on working memory (WM) after an acute sleep restriction, via a decrease of proactive interference sensitivity. The cognitive beneficial effect of ciproxifan in sleep-restricted mice is associated to specific prefrontal cortex area activation.

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